The use of modern biomarkers for the evaluation of the risk of negative outcomes at chronic heart failure

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Abstract

Chronic heart failure (CHF) is a final link in most diseases of cardiovascular system, and despite the successes in the treatment of CHF, mortality remains high, and the prognosis is disappointing.

Currently, the symptoms and objective signs of HF have been described in detail. However, the specific laboratory tests are limited to a single group of markers - natriuretic peptides. The known limitations for natriuretic peptides and the complexity of CHF pathophysiology condition the topicality of searching for other indicators with the aim to search biological and clinical information. In this regard, the biomarkers involved with other pathophysiological mechanisms of CHF appear to be of interest.

A significant role of a new biomarker, stimulating a growth factor ST2, also known as "mechanical" myocardial stress is considered in this article. The mentioned biomarker has shown a high prognostic potential in the patients with HF. The increase of its soluble form sST2 is associated with the depth of the damage, the severity of disease course and its outcome. The assessment of prognostic value of the biomarker determination, as the predictor of cardio-vascular diseases and their outcomes has been performed.

The topicality of searching for new therapeutic drugs in the combination with "traditional" means of CHF treatment is given in this article.

Based on sST2 concentration in the blood, not only CHF degree and effectiveness of performed therapy can be judged, but also more accurately stratify the risk of progressive complications and, thereby, prevent unfavorable clinical outcome.
(TCM-GMJ March 2023; 8 (1):P32-P35)

Keywords: Chronic heart failure; Biomarkers; Soluble form of ST2;

Introduction

Chronic heart failure (CHF) appears to be a final link of the most diseases of cardiovascular system. It is a serious social-economic problem, evidenced by an epidemiological character of the incidence growth all over the world (12, 28). Despite the successes in the treatment of CHF, the lethality remains high, and the prognosis is disappointing (7, 32, 41).

As known, CHF is characterized not only by disorders of heart ability to accumulate or/and empty, but by a compensatory activation of pressor and depressor links of neurohumoral system regulation (19).

Currently, the symptoms and objective signs of CHF have been described in detail; however, specific laboratory tests are limited to a single group of markers - natriuretic peptides. Despite their significance, the levels of these peptides increase along with the age (27), at some acute and chronic conditions (acute coronary syndrome, mitral regurgitation, pulmonary hypertension, obesity, etc.), as well as at the situation accompanying by the increase in cardiac output (23, 29). The above-mentioned limitations for natriuretic peptides and complexity of CHF pathophysiology indicate the topicality of the search of other optimally informative criteria for the evaluation of biological and clinical status. In this regard, along with natriuretic peptides, the biomarkers of another pathophysiological line, responsible for the increase of the risk of negative outcomes in the patients with CHF are of great interest.

The given review deals with the possibility of the use of new biomarkers in the patients with CHF for the evaluation of the risk of negative outcome.

Relatively recently, with this aim the study of suppressor of tumorigenecity of the 2 type (ST2), as a new indicator of unfavorable prognosis has been begun in this group of patients. Protein ST2 is considered a marker of "mechanical" myocardial stress (fibrosis, hypertrophy, cardiac remodeling), expressing genome 2 (Growth Stimulating expressed gene 2) or a stimulating factor of ST2 growth, also known as ILIRLI i/n suppression of tumorigenecity 2 (33). This biomarker has shown a high prognostic potential in the patients with heart failure (HF) (17) and was included in the recommendations of ACC/AHA (40).

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Received June 14, 2023; accepted July 7, 2023.
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Based on the fundamental researches, ST2 belong to the family of interleukin 1 receptors and is seen in two forms: associated with the membranes of target cells ST2 L/ ILIRLI b, i.e. transmembranous receptor and the second - a soluble receptor, observed in blood plasma. The latter form is designated as sST2 (soluble ST2) or ILIRLI a.

ST2 is able to bind to inflammatory mediator – interleukin 33 (IL-33), forming a IL-33/ST2 complex on cardiomyocyte membrane (39). The mentioned complex is able to protect cardiac cells in conditions of hypoxia, to counter the factors of their hypertrophy under angiotensin II action, as well as to decrease in cardiomyocyte fibrosis and reduce the elaboration of natriuretic peptides (34).

The result of effective work of IL-33/ST2 system appears to be a decrease in dysfunction and dilation of the myocardium, inhibition of unfavorable remodeling of the ventricles in response to various damaging factors (24).

ST2 receptor identified in 1959 (38) for many years has been considered as a marker of inflammatory and autoimmune processes. It is known that inflammatory reactions in patients with CHF promote the damage of cardiomyocytes, play an important role in apoptosis process, triggering hibernation of the myocardium and activation of neurohumoral systems of the organism (22).

In 2002 Weinberg et al. (39) reported the expression of ST2 in the culture of cardiomyocytes under the influence of a mechanical stress. They also found a transient increase of the concentration of soluble sST2 isoform in experimental model of myocardial infarction in mice, and the increase of a level of sST2 in the blood of the patients with acute infarction was revealed twenty-four hours after the diseases onset. As an amount of sST2 is inversely proportional to an amount of its bound form, according the level of this marker in the blood one can judge about the effective functioning of IL-33/ST2 system. The increase of sST2 more than 35 ng/ml testifies the depletion of IL-33/ST2 system and predominance of damaging influence on response reparative processes (39).

In subsequent works it has been noted that an excessive increase of ST2 appears to be an independent predictor of mortality and direct indications for heart transplantation. It allowed to putting forward an idea on emergence of a new biomarker of neurohormonal activation of patients with CHF (13, 18).

As was shown, protein ST2 - a member of superfamily of IL-1 receptors play an important role in the regulation of immune and anti-inflammation responses (35).

Protein ST2L consists of 556 amino acids, its molecular weight is 63358 Da. ST2L – membrane binding receptor, the ligand of which appears to be IL-33; ST2L blocks biological effects of IL-33 (36). It is known, that IL-33 has a cardioprotective effect, prevents the development of hypertrophy, fibrosis, counteracts apoptosis of cardiomyocytes by transduction of ST2L (30, 42).

As to sST2 soluble form, its basic source in the blood plasma still remains unidentified both in healthy and in patients with cardiovascular pathology (16). sST2 consists of 328 amino acids, its molecular weight is 36993 Da. Its concentration is determined by immunoenzyme analysis method.

The group of authors has shown that overloading of pressure in mice with ST2L system defect, as well as sST2 leads to more pronounced hypertrophy of the myocardium of left ventricle, the expansion of heart chambers, progression of fibrosis, as compared with control group. The use of recombinant form of IL-33 had a therapeutic effect (hypertrophy regress, reduction of fibrosis) (34). K. Seki et al. (36) supposed that IL-33 is able to prevent cardiomyocytes apoptosis after myocardial infarction.

Based on the given researches the authors revealed that in patients with III-IV functional class (f.c.) of NYHA, sST2 levels were statistically significantly higher, as compared with the patients with I-II f.c. (51 ng/ml, as compared with 25 ng/ml, respectively) (20).

In a number of the studies the data on relationship of sST2 with a severity of structural changes in the heart (3, 6) were obtained.

Although, sST2 concentration in the blood significantly increases at inflammatory processes, onco- and cardiac pathology, but unlike natriuretic peptides does not depend on age and obesity (5, 25, 29). This is its diagnostic value (its advantage).

In multicenter prospective study of PHFS (Penn Heart Failure Study), carried out in 1141 outpatients with systolic CHF, sST2 was shown to be a powerful marker of mortality risk and heart transplantation (11).

A working group of authors concluded that sST2 provides a moderate increase of diagnosis accuracy in relation to traditional clinical predictors and can be useful for detecting patients, needed more aggressive treatment methods (37).

Similar results obtained the researchers from Spain, based on the data of 891 outpatients. According to the data of these authors, as well as the data of BNP (brain natriuretic peptide), the mortality risk was unambiguously predicted at 50 and 1829 ng/ml, relatively. The authors emphasized that simultaneous evaluation of the both biomarkers makes more effective the risk of stratification, thereby the advantage turned out to be on sST2 side. The authors suggest that sST2 may be useful for detecting the patients, needing more aggressive strategies of the treatment (26, 37).

Significant additional data on prognostic role of sST2 are given in the studies of MADHT-CRT (14).

Based on the results of the work, sST2 appeared to be an independent predictor of various complications of CHF, such as attacks of ventricular tachycardia, ventricular fibrillations.

In 2019 the authors published the results of 5-years observation on 744 patients with HF. Out of three studied biomarkers (ST2, NT-pro BNP and highly sensitive troponin), only ST2 was found to be an independent predictor of sudden cardiac death (4).

In CORONA study it has been shown that the analysis of relationship between the dynamics of sST2 concentration and CHF clinical outcome, a decrease in sST2 level was associated with the reduction of hospitalization risk

regarding the impairment of HF. An increase of sST2 by 15.5% and more from a baseline appears to be a predictor of acute decompensation of HF (10).

In MADHT study it is reported that serial changes in sST2 are a predictor of ventricular arrhythmias, each increase of sST2 by 10% leads to a significant increase of development risk of ventricular arrhythmias and death. There are also evidences that an increase of sST2>34.93 ng/ml in the patients with CHF after the implantation of cardioverter defibrillator is closely associated with death caused by cardiovascular disease, decompensation of CHF, acute coronary syndrome or acute disorder of cerebral blood circulation (8).

Based on the data of prospective controlled study PROTECT, including 151 patients with systolic HF, the comparison of three biomarkers sST2, BNP and a factor of differentiation growth (GDF), sST2 has shown the greatest dynamics as compared with the others, sST2 appeared to be the only one, providing an additional prognostic information at serial testing. The results obtained after 3- and 6 months increased the power of the prognosis of baseline data (9).

Prognostic value of serial changes in sST2 was studied by C. Bahuleyon et al. (2018) (10) in prospective multicenter research, including 141 patients with III-IV f.c. (NYHA). The concentration of sST2 in baseline condition was reliably higher among the patients with unfavorable events, as compared with the patients without undesirable events. ROC analysis for initial sST2 concentration identified a magnitude at 49 ng/ml, as an optimal value for the prognosis of negative outcomes. It has been shown that initial sST2 concentration appears to be an independent predictor of negative outcome. sST2 concentration was reliably correlated with negative outcomes. The authors indicate a close relations with clinical outcomes of sST2 levels and other control points (2).

Based on Russian researcher's data (1), a clear advantage of sST2 is noted, as compared with other new biomarkers of HF. The authors indicate the necessity of decrease in sST2 level (<30 ng/ml) for the improvement of prognosis (21). It should be noted that Grokov et al. (2019) (2), in their work demonstrated that the determination of sST2 content in the blood before and after 6-minute walk test allowed increasing specificity and sensitivity of stratification risk method for the development of unfavorable cardiovascular events (15).

It is known that the blockade of neurohumoral activity significantly improves clinical outcomes in the patients with CHF. Nevertheless, the available data testify that for various reasons a lot of patients either are not treated with these drugs, or are treated in doses below the recommended. It makes impossible to improve the results of treatment (19, 31, 43). So, in PROTECT study an impact of achievement of target doses of beta-blockers on clinical outcomes were studied.

In the patients with CHF depending on initial level of sST2 (low ≤35 ng/ml, as compared with high >35 ng/ml), it turned out that in patients with a low level of sST2 and a high dose of beta-blockers the number of developed negative cardio-vascular episodes was the least. The most unfavorable group consisted of patients with initial high concentration of sST2 and a low dose of beta-blockers.

Particularly noteworthy were the data obtained in multicenter, randomized, double-blind studies PARADIGM-HF, regarding a new combined pharmacological means for treatment of patients with HF – inhibitor of neprelisin-sacubitril and a blocker of angiotensin II receptor – valsartan/sacubitril/valsartan. The study involved 8399 patients. A complex analysis of predictors of initial concentrations of sST2 increase has been carried out for the first time. Among these predictors the most significant were increase of BNP level, male gender and atrial fibrillation in anamnesis. The increase of sST2 after 1 month was directly associated with negative outcomes and, conversely, a decrease in sST2 had a positive clinical results. In the patients of sacubitril/valsartan more pronounced decrease in sST2 concentration was observed, as compared with the patients of enalapril group (31). 8 months after the randomization, a decrease in sST2 concentration was more observed in sacubitril/valsartan group, as compared with enalapril group. At this control point, the dynamics of sST2 associated with the changes in clinical data, as compared with initial levels (31, 43).

Thus, generalizing above-said it has become clear that a timely determination of sST2 biomarkers activity allows optimizing therapeutic process, determination the patients with a high risk of disease progression and, thereby, avoid unfavorable clinical outcome.

Summary

Chronic heart failure (CHF) is a final link in most diseases of cardiovascular system, and despite the successes in the treatment of CHF, mortality remains high, and the prognosis is disappointing.

Currently, the symptoms and objective signs of HF have been described in detail. However, the specific laboratory tests are limited to a single group of markers - natriuretic peptides. The known limitations for natriuretic peptides and the complexity of CHF pathophysiology condition the topicality of searching for other indicators with the aim to search biological and clinical information. In this regard, the biomarkers involved with other pathophysiological mechanisms of CHF appear to be of interest.

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